뇌신경질환 치료제 후보발굴 비임상 효능 평가, 부작용 검증 및 중독 평가 서비스 플랫폼

Listen to your “Need“

“Bespoke” CDRO service

Until you say “Yes "

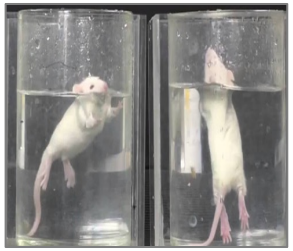
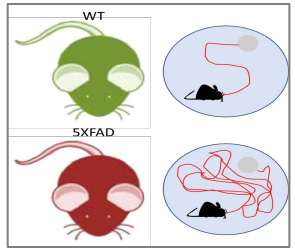
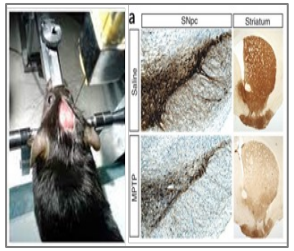
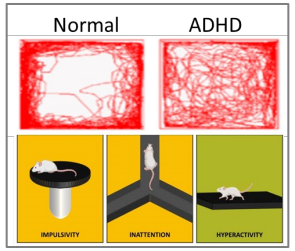
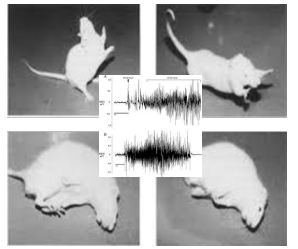
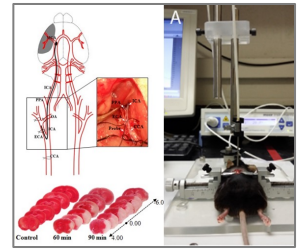
NeuroVenti

NeuroVenti

목차

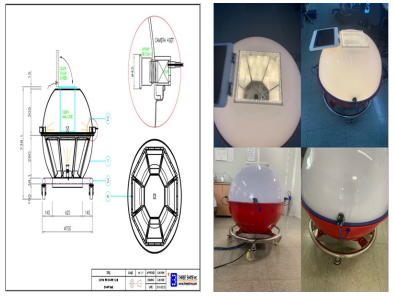
1. 뇌신경 질환 동물모델

구축된 뇌신경질환 동물 모델

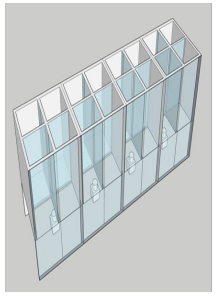
우울증	알츠하이머병/ 치매	파킨슨병	조현병	자폐스펙트럼장애	주의력결핍 과잉행동장애	뇌전증	뇌졸중
							
• Acute restraint stress, Chronic mild stress, Maternal deprivation • Corticosterone/LPS-injection	• Genetic: 5xFAD Tg mice • Aβ/scopolamine/LPS injection, DM-induced dementia model, BCCAO	• 6-OHDA/ rotenone/MPTP injection • α-synuclein overexpression • A53T Tg mice	• MK-801/ PCP/ amphetamine/ Poly(I:C)-injection • Social stress model (social isolation, social defeat)	• Genetic : CNTNAP2 KO, Fmr1 KO mice, AGMAT Tg mice • Chemical : VPA/Poly(I:C)-injection	• Genetic: SHR, Fmr1 KO • Chemical: EtOH/MK-801-injection	• Electricity induced model (MES) • Chemical induced model (PTZ, KA, Bic) • Kindling • Febrile sz • Sz-prone animals	• Photothrombosis-induced model, MCAO • ET-1/ Hemin/ autologous blood injection

2. in vivo 효능 평가 자동화 분석 시스템

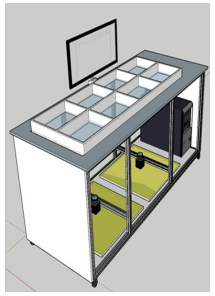
in vivo 효능 평가 및 부작용 검증 평가 시스템 (AI 기반 행동 분석 시스템)



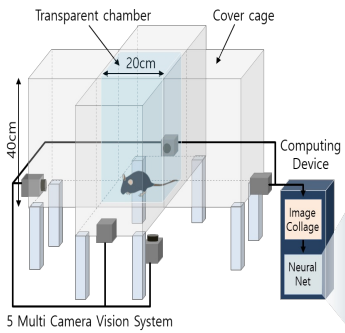
3차원 행동 분석 관측장비

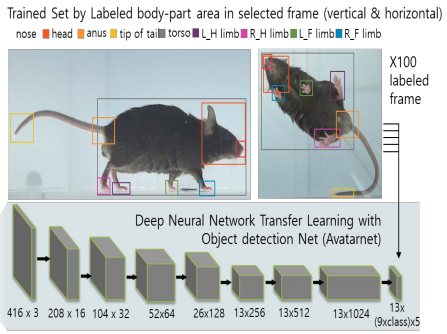


다중개체 동시 분석장비



연구자 동시 관찰 장비





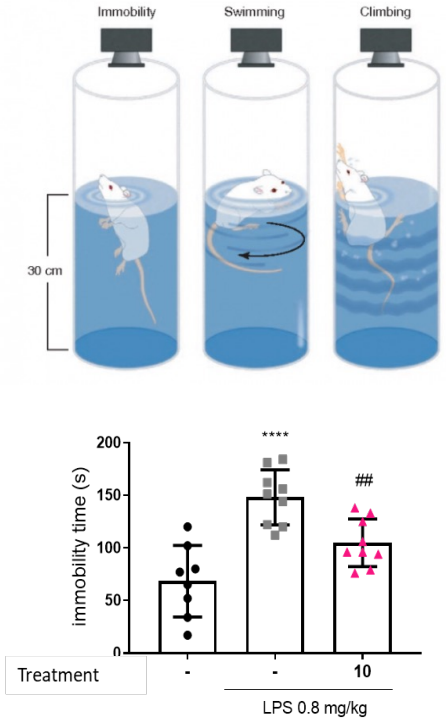
효능평가			
행동 도메인	평가방법	행동 도메인	평가방법
사회성, 의사소통	Three chamber test, Home-cage social test, Ultra sonic vocalization test	기억,학습	Barnes maze test, Y-maze test, Novel object recognition test, Passive avoidance test, Morris water maze test
반복행동	Self-grooming test, Marble-burying te st, Nest building test	우울행동, 불안	Forced swim test, Tail suspension test, Sucrose preference test, Open field test, Novelty suppressed feeding test, Elevated plus maze test, Light dark box test
행동기능	Open field test, Rotarod test, Footprint test, Beam walking test Grip strength test, Pole test, Grid hanging test, Grid waking test,	충동성	Cliff avoidance test, 5-choice serial reaction time test, Delayed discounting test

부작용평가	
평가 도메인	평가방법
의존성	조건장소 선호도 평가 자가 투여시험
수면 장애	수면시험 (입면시간, 수면지속시간측정) 뇌파측정(EEG telemetry)
감각운동 게이팅	선행자극 억제 시험
경련	Chemical, Electricity induced seizure, threshold, 뇌파측정(EEG telemetry)

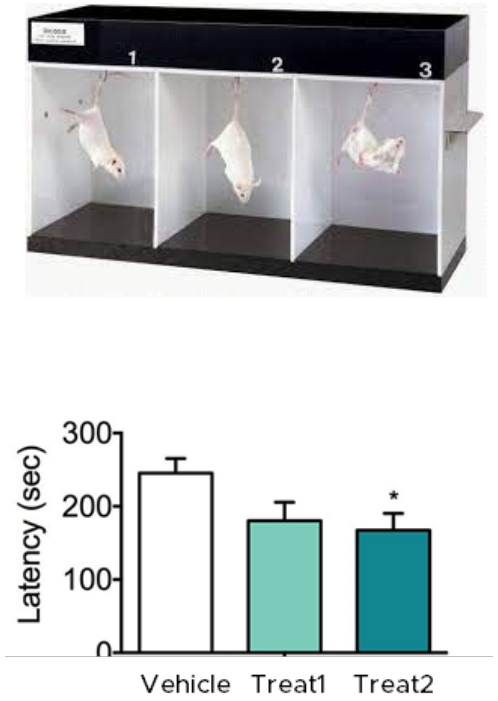
2-1. 우울증 치료제 개발 및 효능 평가 in vivo 시스템

우울증 (Depression) 주요 행동 평가

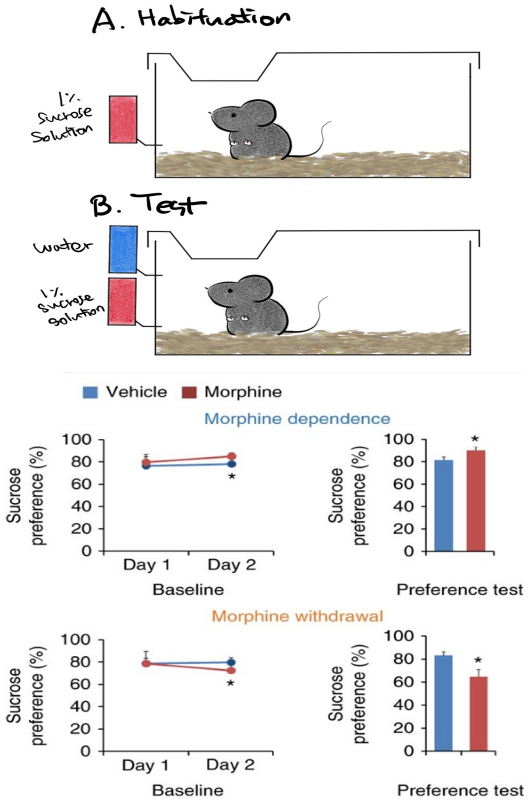
Forced swim test



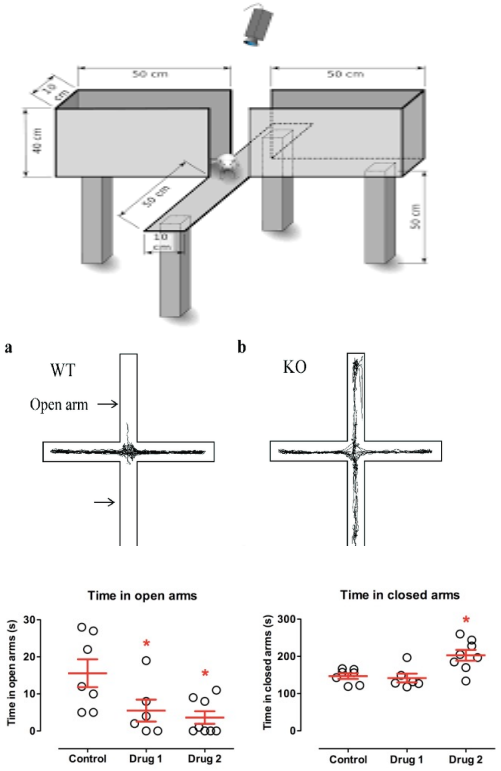
Tail suspension test



Sucrose preference test



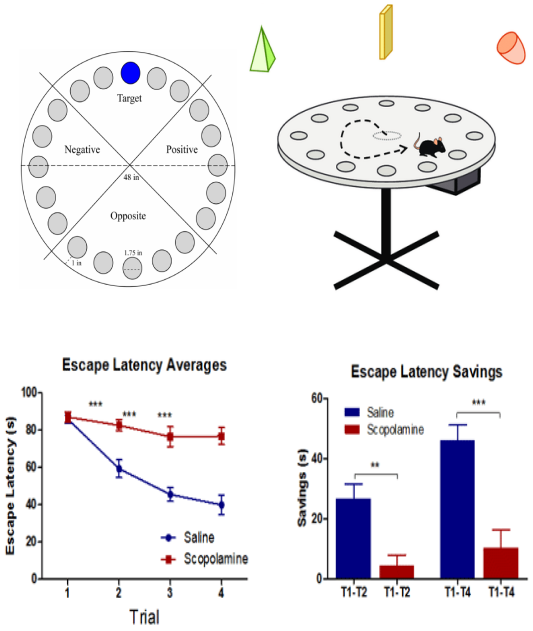
Elevated plus maze test



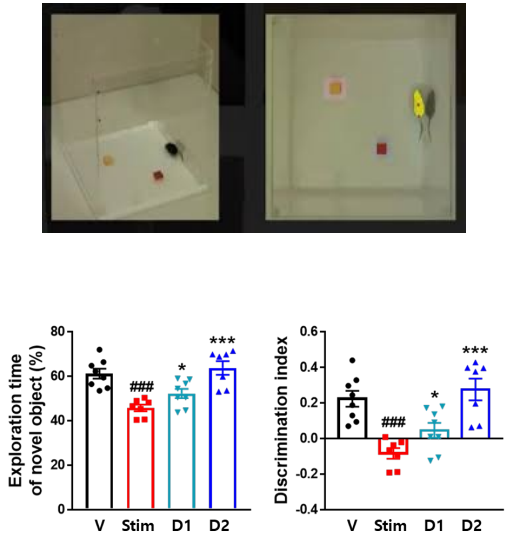
2-2. AD 치료제 개발 및 효능 평가 in vivo 시스템

알츠하이머병/치매 (AD/Dementia) 의 주요 행동 평가: 인지기능

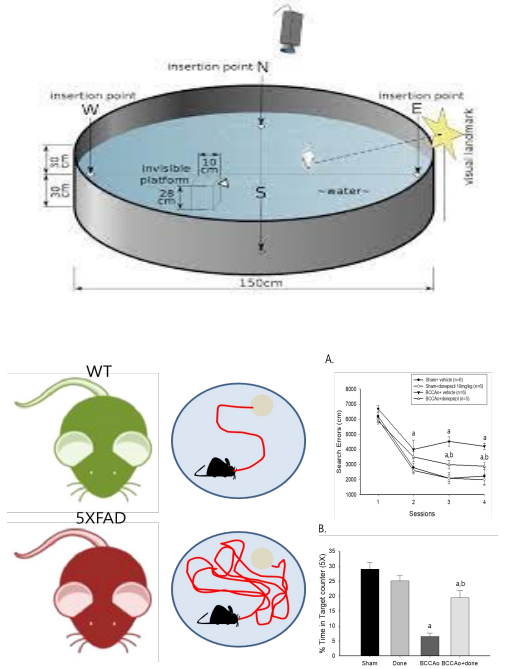
Barnes maze test



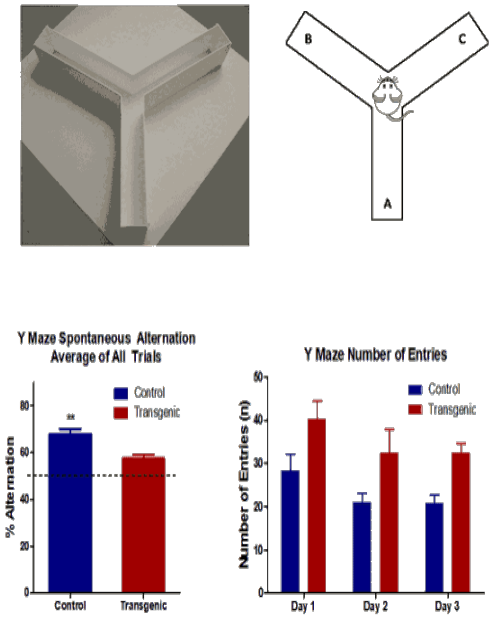
Novel object recognition test



Morris water maze test



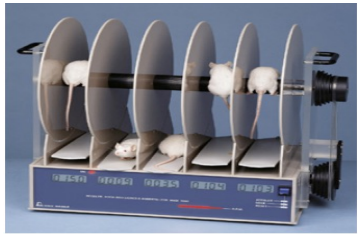
Y maze test

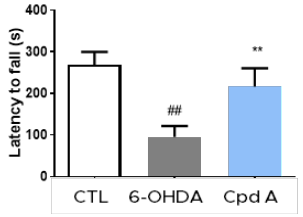


2-3. PD 치료제 개발 및 효능 평가 in vivo 시스템

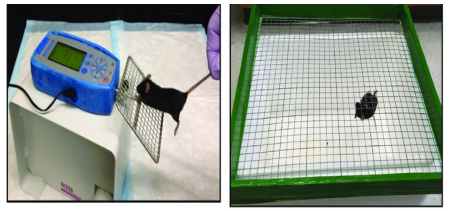
파킨슨병 (PD)의 주요 행동 평가 : 운동기능, 운동 협응

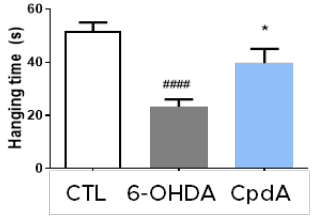
Rotarod test



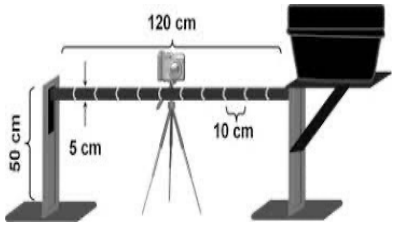


Grip strength & Grid hanging test

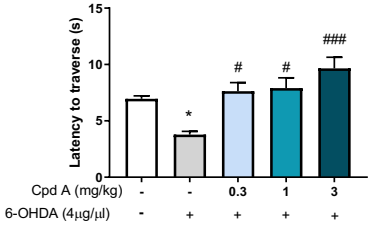




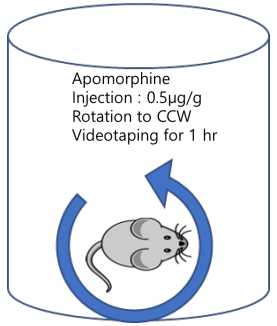
Beam walking test

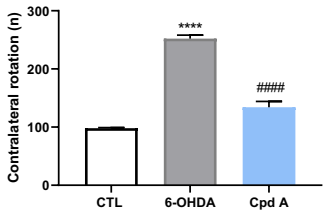


Number of foot slips,
time to traverse beam(s)

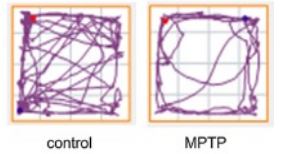


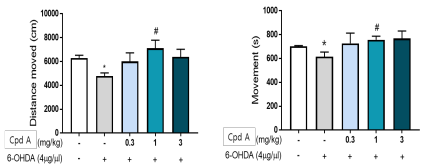
Rotation test





Open field test



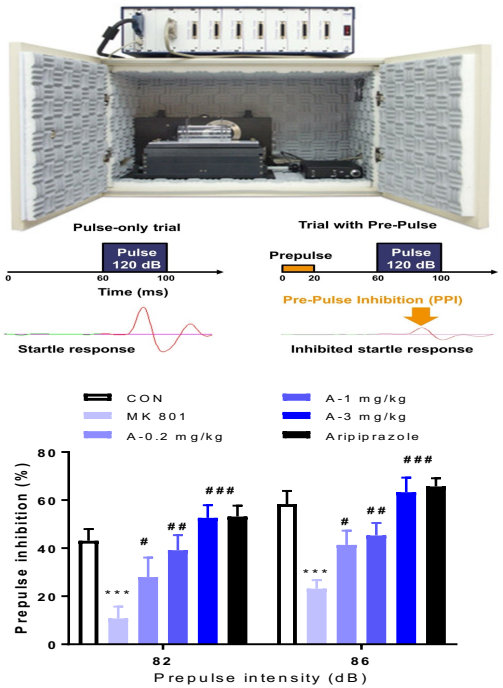


2-4. 조현병 치료제 개발 및 효능 평가 in vivo 시스템

조현병 (Schizophrenia) 주요 행동 평가

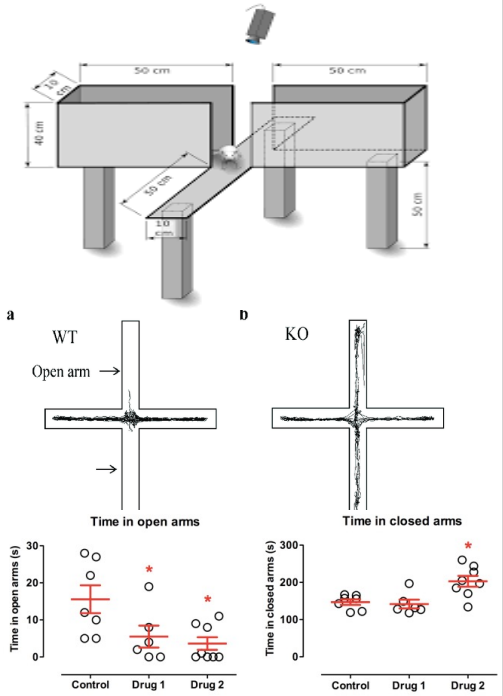
감각운동 게이팅

Prepulse inhibition test



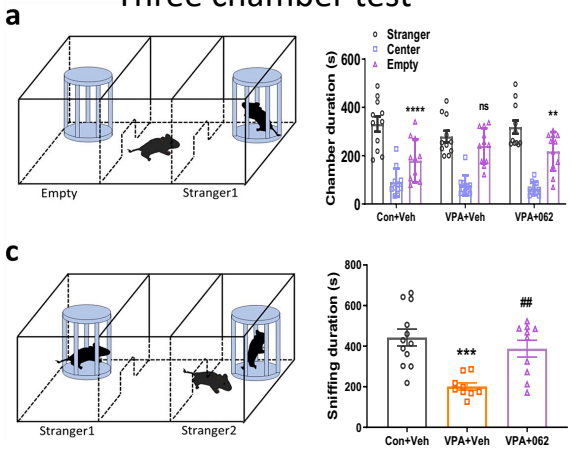
불안

Elevated plus maze test

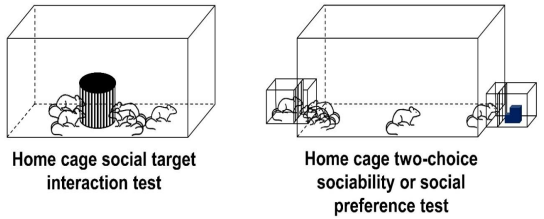


사회적 상호작용

Three chamber test

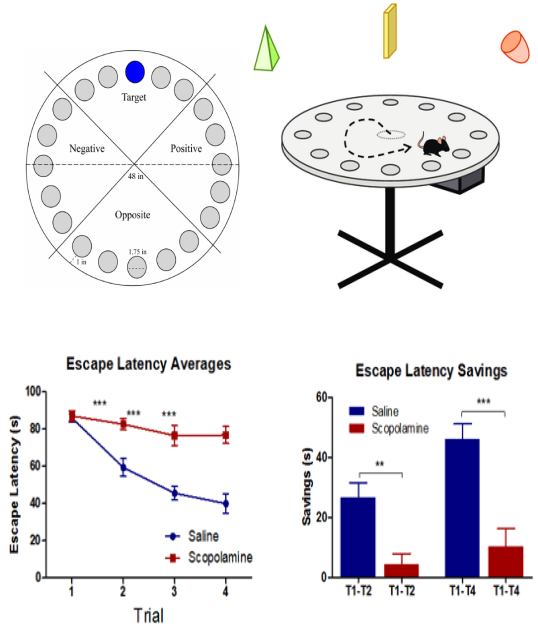


Home cage social test



기억/인지기능

Branes maze test

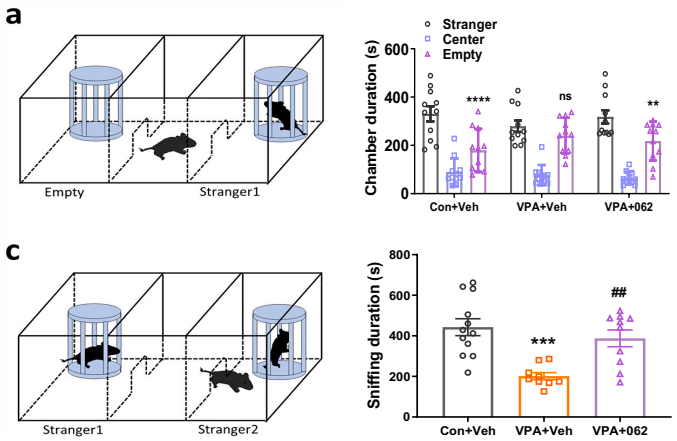


2-5. ASD 치료제 개발 및 효능 평가 in vivo 시스템

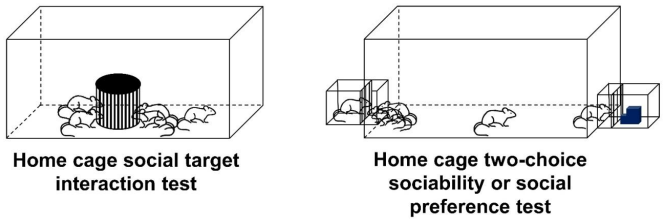
자폐스펙트럼장애 (ASD) 주요 핵심 증상 행동 평가 : 사회성, 의사소통, 반복행동

사회적 상호작용

Three chamber test



Home cage social test

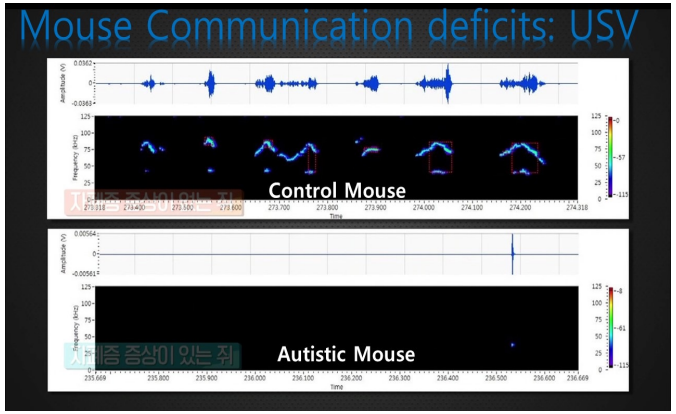


Home cage social target interaction test

Home cage two-choice sociability or social preference test

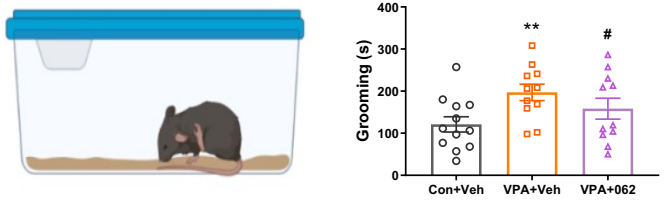
의사소통

Ultrasonic vocalization test

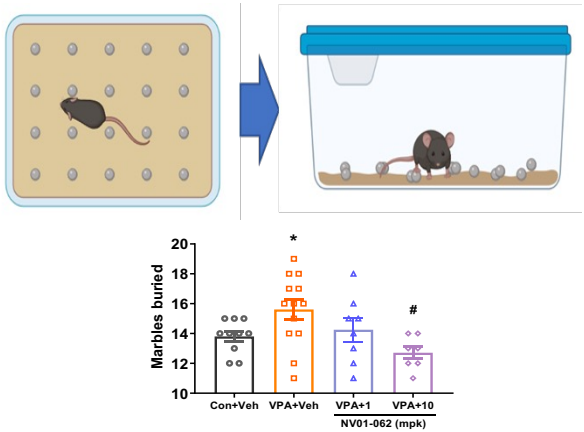


반복행동

Self-grooming test



Marble burying test

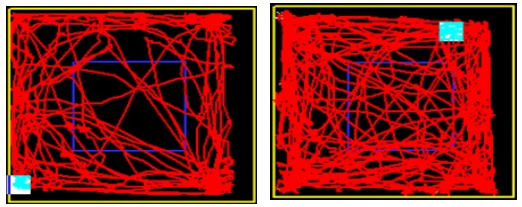


2-6. ADHD 치료제 개발 및 효능 평가 in vivo 시스템

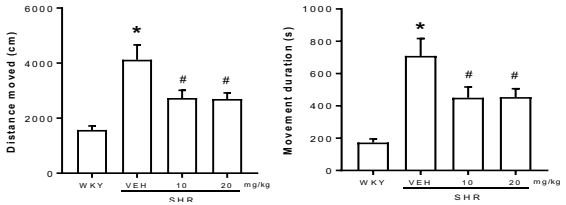
주의력결핍 과잉행동장애 (ADHD) 주요 핵심 증상 행동 평가 : 과잉행동, 집중력, 충동성

과잉행동

Open field test

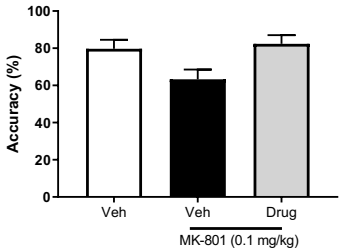


Control ADHD

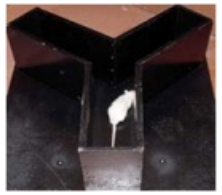


집중력

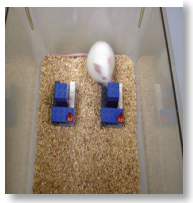
5-choice serial reaction time test

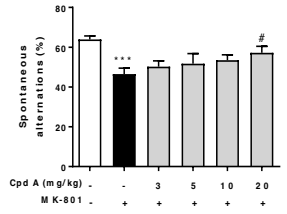


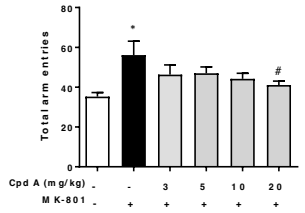
Y-maze test



Object recognition test

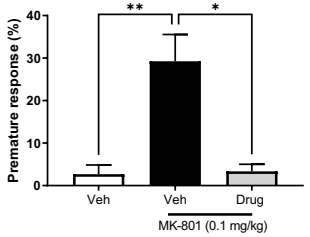




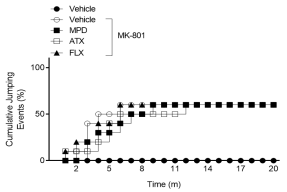


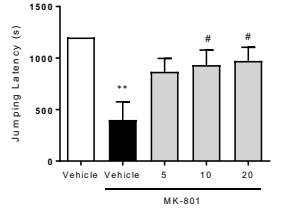
충동성

5-choice serial reaction time test



Cliff avoidance test



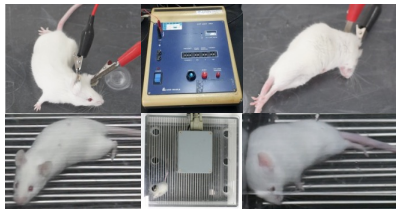


2-7. 뇌전증 치료제 개발 및 효능 평가 in vivo 시스템

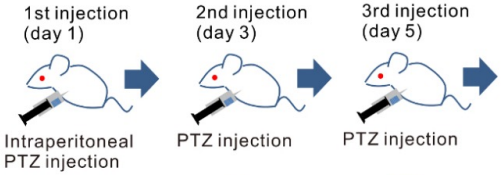
뇌전증 관련 주요 효능 평가 : 경련, 뇌파, 사회성, 기억

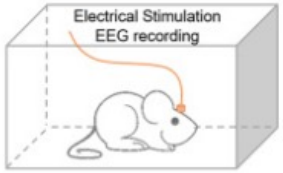
동물모델	경련	사회성/불안	기억/학습

Electricity induced seizure

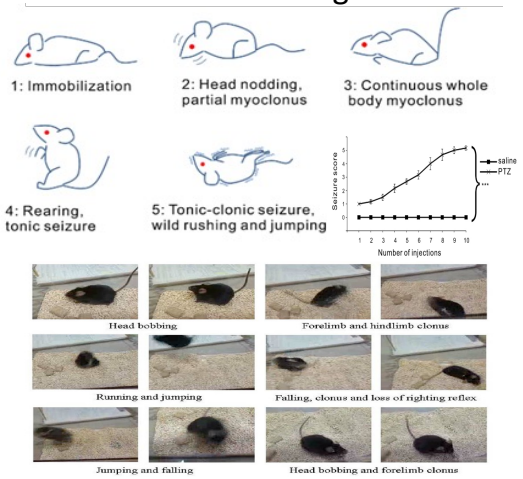


PTZ- induced seizure

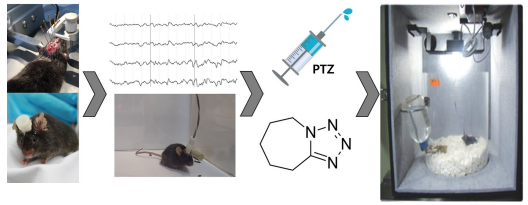




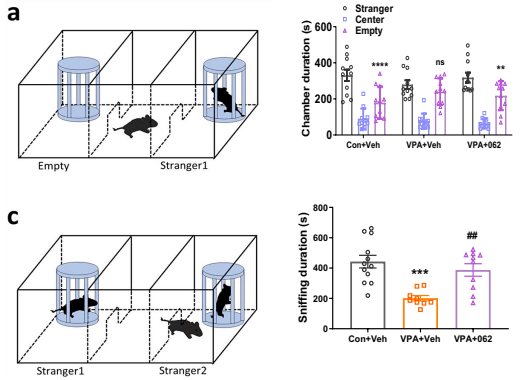
Seizure scoring



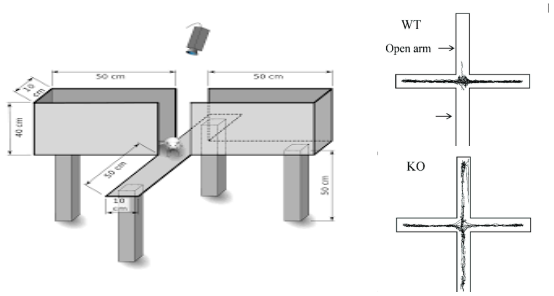
Telemetric EEG recording



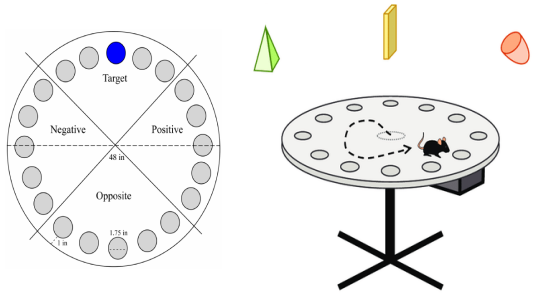
Three chamber test



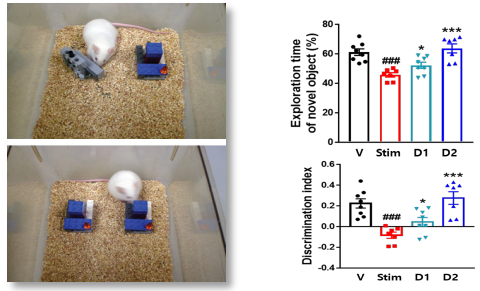
Elevated plus maze test



Branes maze test



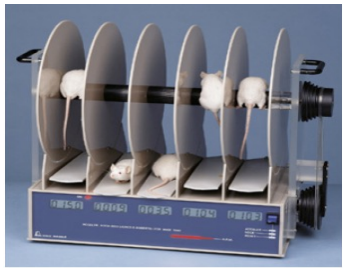
Novel object recognition test

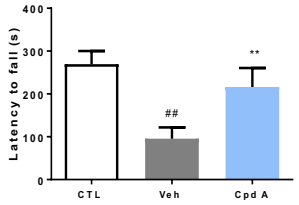


2-8. 뇌졸중 치료제 개발 및 효능 평가 in vivo 시스템

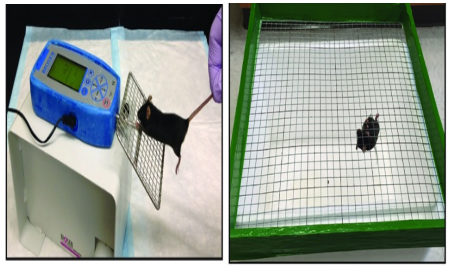
뇌졸중 주요 행동 평가 : 운동 기능, 운동 협응

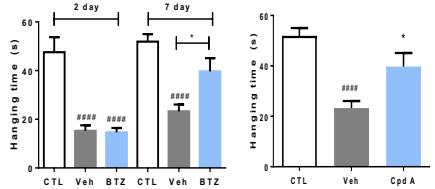
Rotarod test



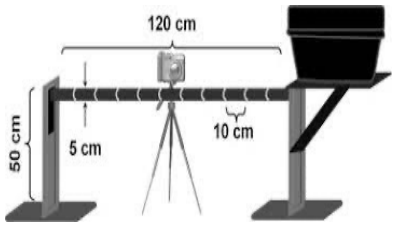


Grip strength & Grid hanging test

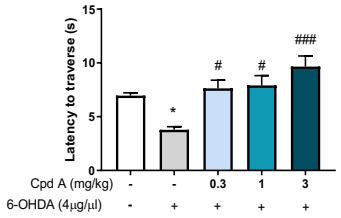




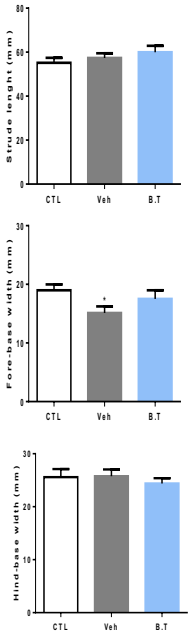
Beam walking test

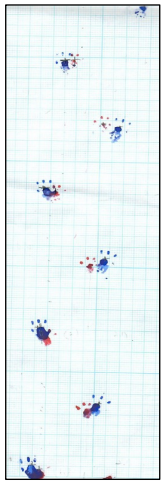


Number of foot slips,
time to traverse beam(s)

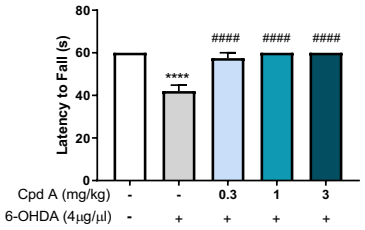


Foot print test





Grid walking test

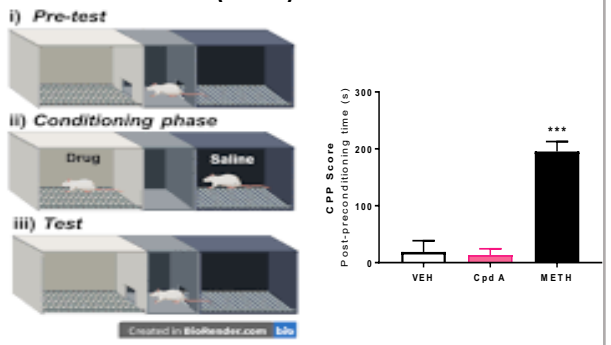


3. 중추신경계 부작용 검증 시스템

부작용 검증 평가: 의존성, 수면, 감각운동 게이팅, 경련

의존성

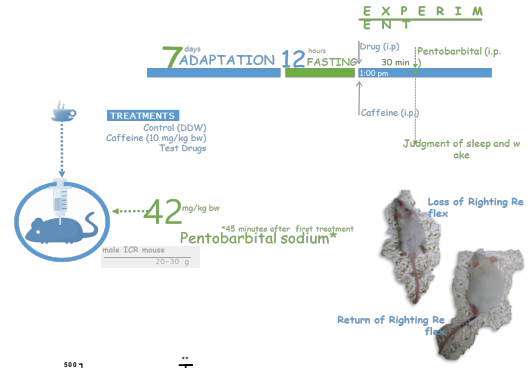
Conditioned place preference (CPP) test

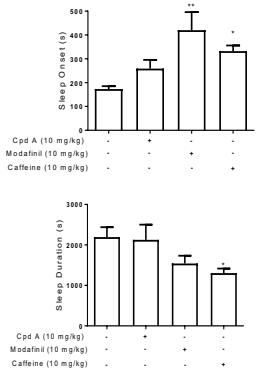


Self-administration (SA) test

수면장애

Sleeping test

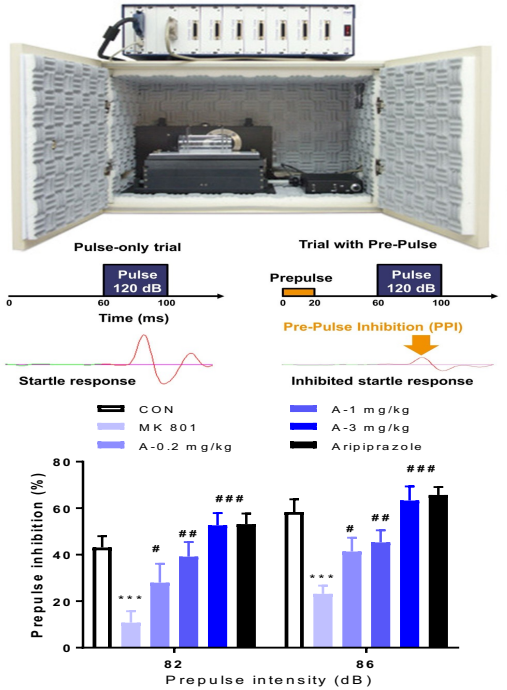




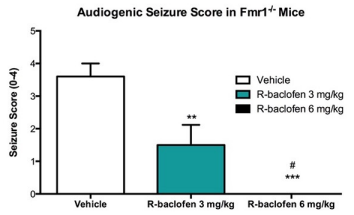
EEG

감각운동 게이팅

Prepulse inhibition test



경련



4. 중추신경계 의존성 유발 및 중독 검증 시스템

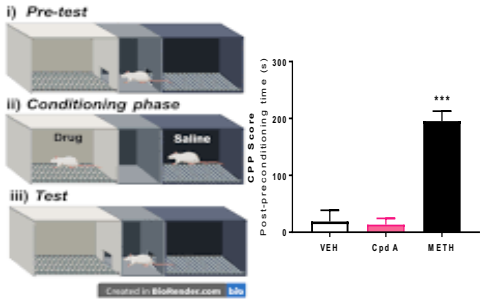
평가 도메인	평가방법	
수용체 결합시험	도파민수용체 결합시험, 도파민 재섭취 시험, GABA수용체 결합 시험, 염소이온 유입시험 노르에피네프린 및 세로토닌 재섭취 시험, opioid 수용체인 μ, δ, κ-수용체에 대한 결합 시험 카나비노이드 수용체 CB1, CB2에 대한 결합시험	중추신경계 흥분제 진정수면제, 전신 마취제, 항불안제 및 항우울제, 마약성 진통제, 카나비노이드 유도체
정신적 의존성	조건장소 선호도 평가 (Conditioned place preference test) 자가 투여시험(Self administration test)	
신체적 의존성	자발 운동량 시험 (만성투여 후 약물 사용 중단; Locomotor test, Prepulse inhibition test, Treadmill test), 경련 반응, 도약시험 (Cylinder test), Climbing test (도파민), Head twitch test (세로토닌), 금단행동 (Rotarod test, Open field test, Elevated plus maze test)	
금단증상	불안 (Elevated plus maze test), 인지 (Novel object recognition test), 우울행동 (Forced swim test) 평가, 선행자극 억제 시험 (Prepulse inhibition test)	
약물 변별	약물구별 시험 (drug discrimination test)	
수면 장애	수면시험 (Pentobarbital-induced 수면유도모델, Caffeine-induced 수면박탈모델, REM sleep deprivation model) 뇌파측정 (EEG)	
민감도	무쾌감증 (Sucrose preference test)	
경련	발작 강도 측정, 발작 발현시간, 경련 지속시간, 회복시간 측정, 발작 행동 측정 Electrically-induced model, chemically-induced model, 뇌파측정 (EEG)	

4-1. 중독 평가 시스템 1

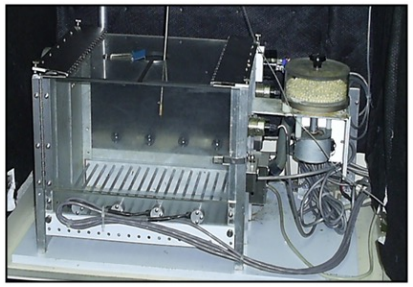
- 중추신경자극제 (methylphenidate, 식욕억제제, amphetamine 류), 중추신경억제제 (Benzodiazepine, Barbiturate류, 수면/진정제 등), 마약성 진통제 (Opioids 류), 환각제류 (MDMA, LSD, PCP, Psilocybin 등), 기타 (카나비노이드, 니코틴류 등)

의존성

Conditioned place preference test

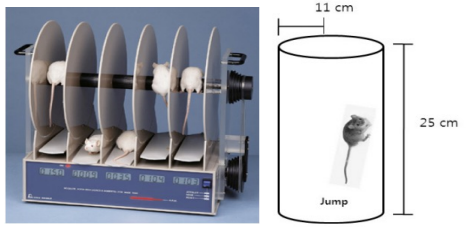


Self-administration test

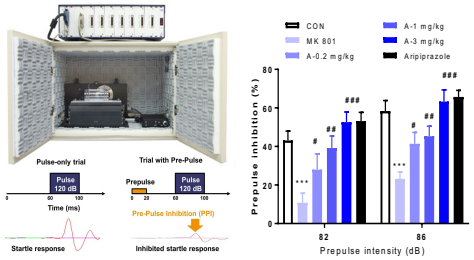


금단증상 1

Rotarod test 도약시험



Prepulse inhibition test



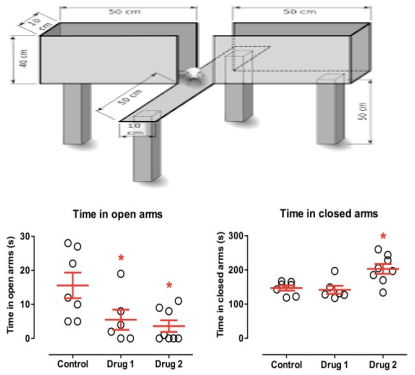
금단증상 2

Locomotor: OFT

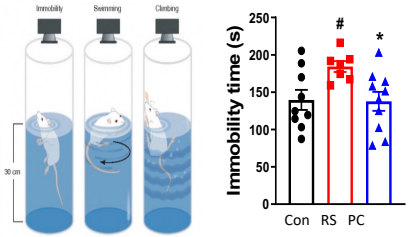
Climbing Behavior Test

불안, 우울

Elevated plus maze test

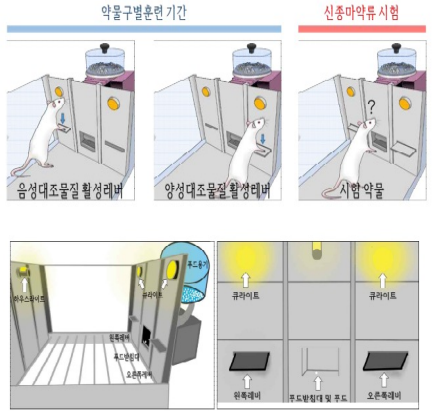


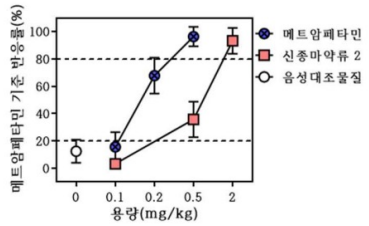
Forced swim test



약물 변별

Drug discrimination test

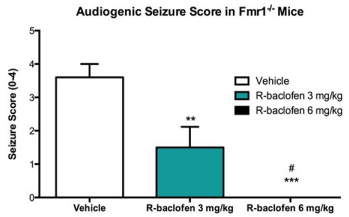




4-2. 중독 평가 시스템 2

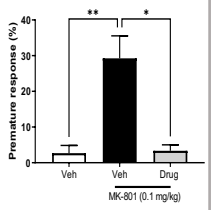
경련반응

Seizure scoring

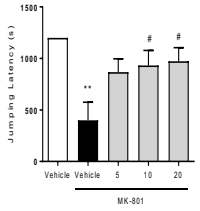


충동성

5-choice serial reaction time test

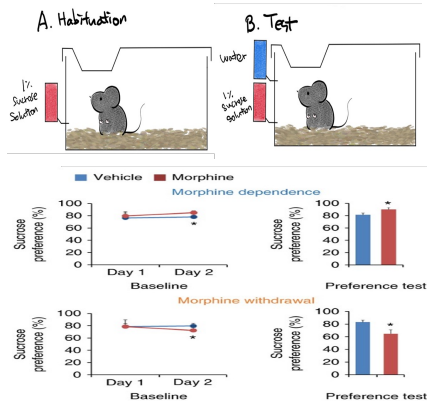


Cliff avoidance test

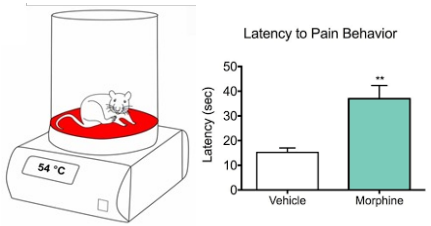


민감도

Sucrose preference test

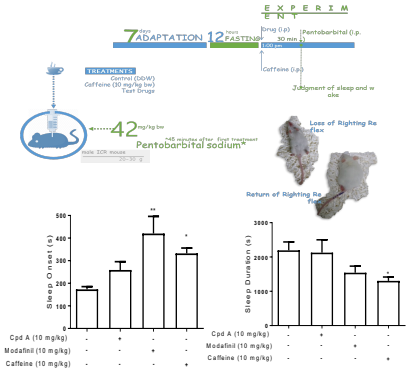


Hot plate test

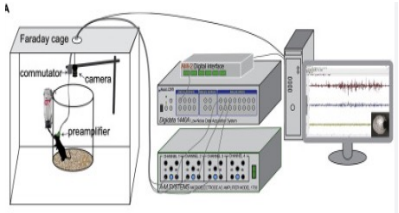


수면

Sleeping test



EEG



머리 흔들기

Head-twitch response

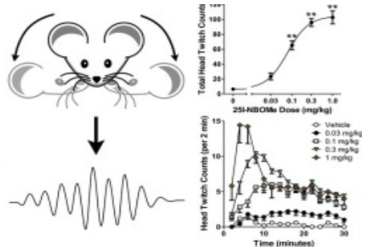


Table 1. *Compounds that produced head-twitches in mice*

Compound	ED50 and 95 % limits (mg base/kg s.c.)		Time of max. effect (min)
LSD	0.045	0.025–0.080	9–11
MLD	0.074	0.058–0.11	4–6
Ergometrine	10	6.7–15	14–16
Psilocin	1.3	0.67–2.2	4–6
Psilocybin	1.1	0.55–2.0	4–6
DMT	2.8	0.74–8.0	2–4
Bufotenin	15	11–21	14–16
dl-α-Methyltryptamine	7.9	3.4–18	44–46
5-HTP	75	50–105	9–11
Mescaline	9.6	4.7–17	19–21
α-Methylmescaline	11	6.0–23	14–16
α-Ethylmescaline	20 approx.	—	14–16
DMPE	15	9.2–27	9–31
Hyoscine	4.2	1.8–7.2	9–11
Atropine	8.9	4.2–15	2–16
Benzhexol	7.6	4.5–16	14–16
JB329	11	6.9–16	4–6
Phencyclidine	0.36	0.17–0.62	4–21
Yohimbine	8.4	3.7–14	14–31

5. in vitro 효능 검증 및 기전 연구 시스템

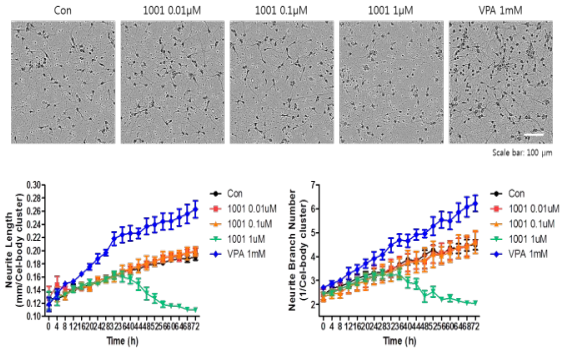
항목	평가방법
세포배양모델	Primary neurons/astrocytes/microglia culture, Neuronal precursor cell culture Organotypic brain slice culture
활용 세포주	HT22, Neuro2A, N27, SH-SY5Y, PC12, C6 glioma, BV-2, bEnd.3 cell
신경세포사멸 및 신경세포 분지조절	Incucyte zoom live cell imaging system
미토콘드리아 기능 조절	OCR : Seahorse XF Cell Mito Stress Analyzer system Fusion/Fission : ICC (Drp1 and PGC1alpha) Biogenesis : TIMM23, TOMM20, SDHA, COX4, PDK4, SMAC expression, mtDNA ROS : mitoSOX, Mitotracker, TMRM
신경전달물질 변동	Fast scan cyclic voltammetry Functional reuptake assay (NET, SERT, DAT)
시냅스생성 및 변화	Morphology: EM, Confocal imaging Alternation of synapse protein: WB, IHC/ICC (PSD95, synaptophysin, synapsin, SNARE etc)
신경발생 및 분화 조절	Proliferation: Immunostaining(Ki-67, BrdU, Nestin, doublecortin) Differentiation: tPA/PAI-1/MMPs zymography system, Immunostaining(Tuj-1, NCAM, BDNF)
뇌혈관장벽 투과	Immunostaining: Tight junction molecules, GFAP, vWF, NG2, PDGF BBB integrity: Evans blue dye, IgG extravasation, brain edema
항산화작용 및 신경염증조절	Antioxidant enzyme: HO-1, GSH, NQO1 ROS measurement: DHE, $DCFH_2DA$, Rhodamine, MDA, 4-HNE Expression and release of Inflammatory cytokine: RT-PCR, WB, ELISA
신규타겟발굴	RNA Sequencing, PCR Array, Epigenome analysis, Real time-PCR

5-1. in vitro 효능 검증 및 기전 연구 시스템 I

Evaluation system for in vitro efficacy and mechanism study I

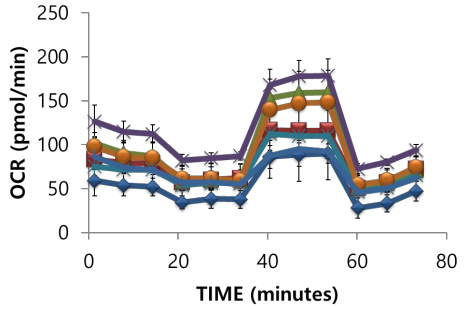
신경세포보호 및 신경돌기성장

Incucyte Zoom Live cell imaging



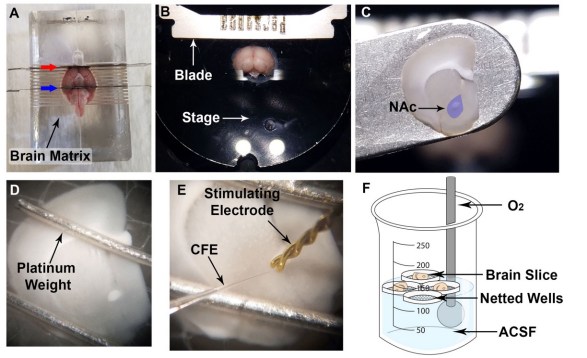
미토콘드리아 기능

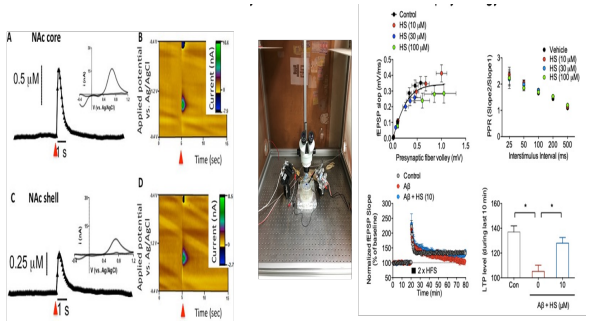
Seahorse XF Cell Mito Stress Test



신경전달물질변화

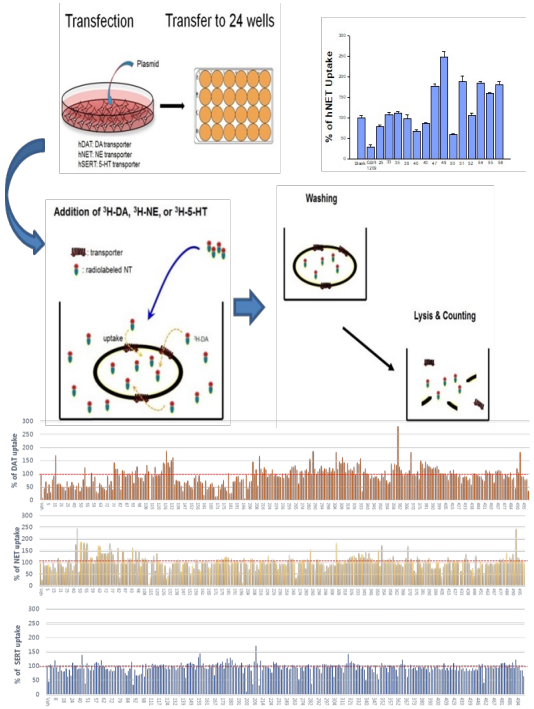
Fast scan cyclic voltammetry





신경전달수송체 기능

Functional reuptake assay

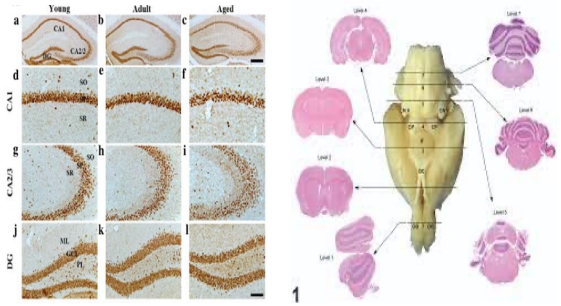


5-2. in vitro 효능 검증 및 기전 연구 시스템 II

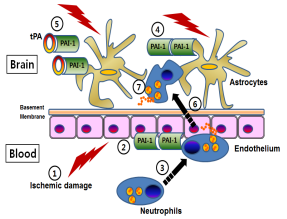
Evaluation system for in vitro efficacy and mechanism study II

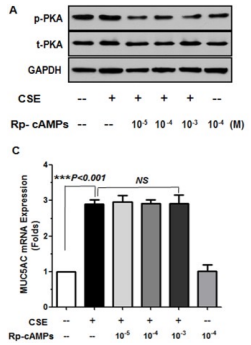
신경재생 및 분화

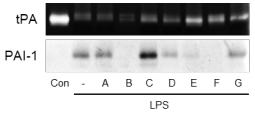
Immunostaining



Proteinase activity & expression

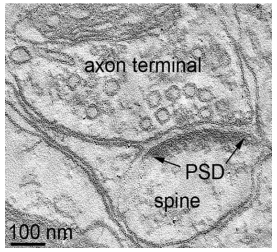


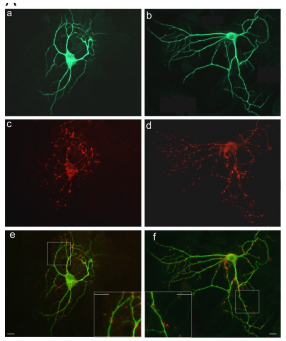




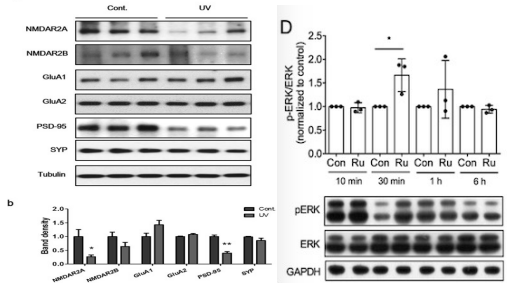
시냅스 생성

Morphology change



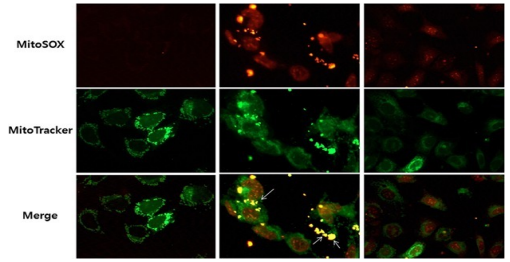


Synapse protein expression

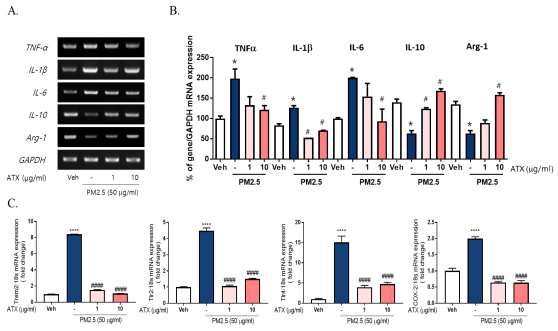


신경염증/ROS

Mitochondrial ROS imaging

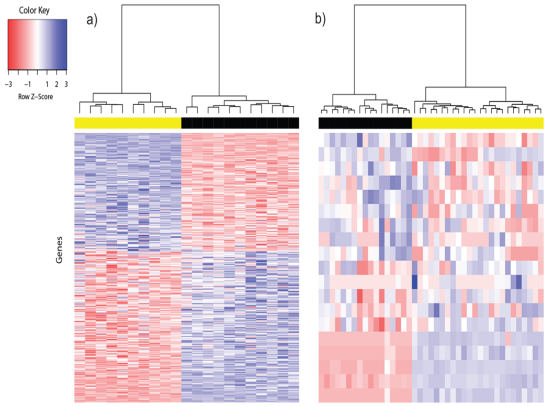


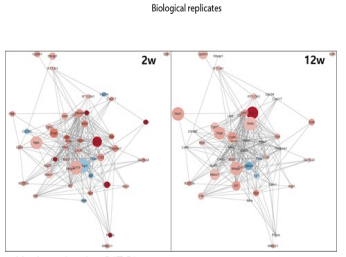
Inflammatory cytokine release

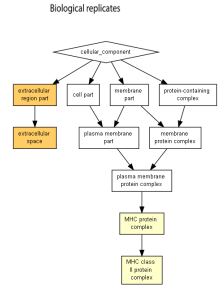


신규타깃 발굴

RNA sequencing







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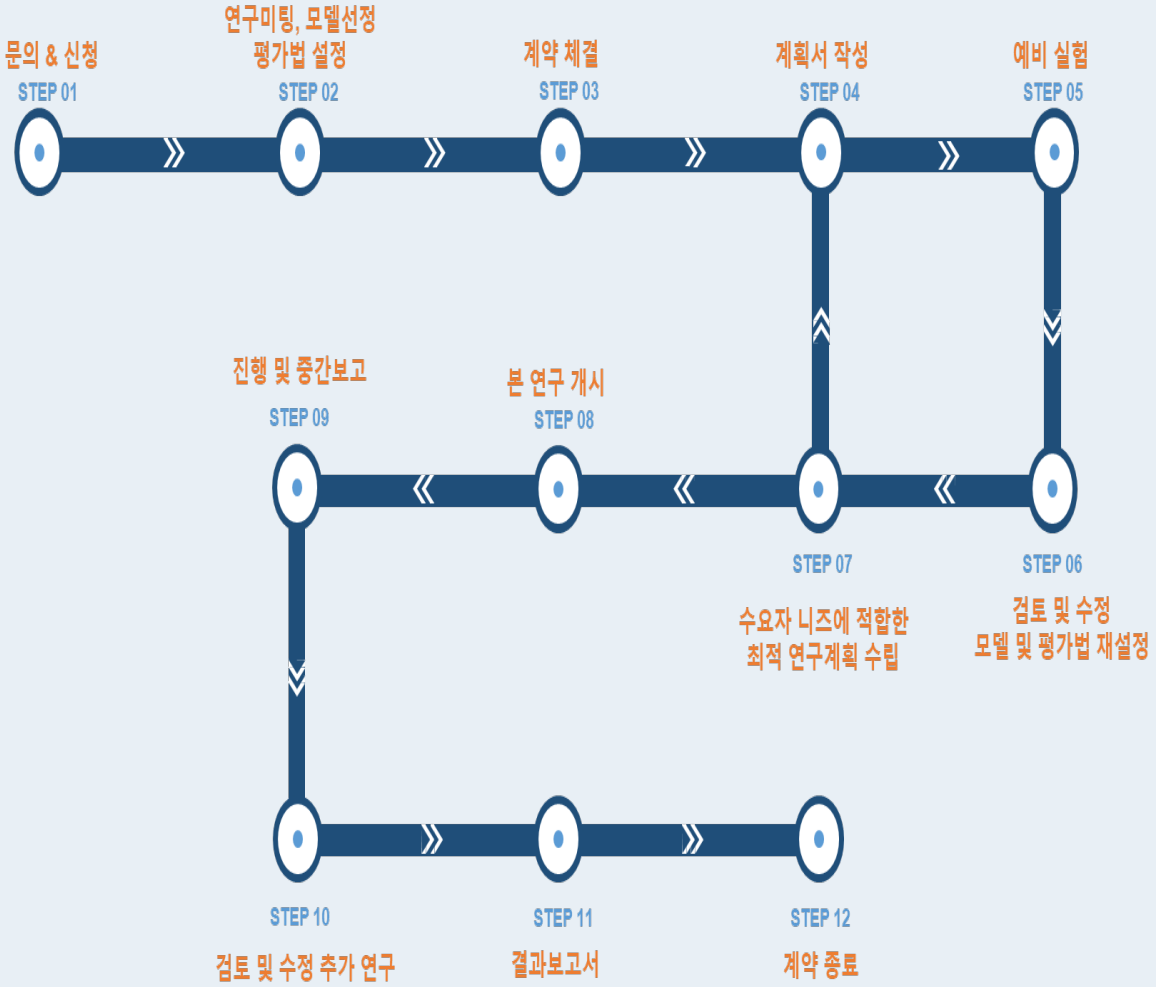
Node size: p-value

6. 공동연구 및 연구개발 서비스 신청 절차

- 다양한 뇌질환 모델, in vivo 효능평가 및 기전 연구 시스템, in vitro 효능평가 및 기전연구 시스템 확보
- 공동 연구 및 연구개발 서비스 문의 신청 후 상담을 통해 모델선정, 예비실험, 평가법 설정
- 수요자 니즈에 적합한 최적의 연구계획 수립

- 서비스 및 연구상담 신청, 자문 컨설팅 의뢰 및 기술 문의 등은 ㈜ 뉴로벤티 기업부설연구소로 연락주십시오.



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THANK YOU

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